AD650415

Reprinted from ANGIOLOGY
Vol. 18, No. 1 January, 1967

THROMBOPHLEBITIS AND BASIC VASCULAR PROBLEMS*

ROBERT M. HARDAWAY, III, COLONEL, MC, USA

The most important and basic vascular problem is the maintenance of fluidity of the blood to enable an adequate flow through blood vessel lumen. If blood clots, flow stops. Clotting of blood may not only cause a temporary stoppage of flow directly, but may play a part in the etiology of permanent obliteration of the lumen. In addition, parts or all of the clot may break off and obstruct distant sites such as the pulmonary circulation. It is the purpose of this paper to point out factors which influence the blood to clot in the blood vessels.

In general there are four factors concerned with clotting of the blood within blood vessels. These are (1) blood flow, (2) blood coagulability, (3) substances which may initiate coagulation and (4) the condition of the endothelium. Abnormalities in any of these areas may cause intravascular coagulation. A combination of these abnormalities may cause them to aggravate each other in a vicious circle.

BLOOD FLOW

Blood flow is influenced by numerous factors. Slow or inadequate flow predisposes to coagulation. The reason for this is not entirely known but is in part related to the increase in viscosity with slowing of flow. In addition, slow flow through capillaries results in acidosis and altered coagulability, as described below. Of course, flow through veins is much slower than that through arteries due to the decreased pressure and the greater diameter of the veins. This alone makes veins more subject to thrombosis than arteries. Some of the factors which influence blood flow follow.

Gross mechanical factors. Flow of blood through the veins is adversely affected by pressure on the pelvic veins of a pregnant uterus, tumors, and the like, standing still, sitting still, lying still, dependency of legs and many other mechanical causes.

Decreased cardiac output. This can in turn be due to a variety of causes. One common cause is inadequate venous return to the right heart via the vena cavae. This may be secondary to many different factors. Acute hemorrhage or hypovolemia cause an insufficiency of blood in the vascular tree. This results in insufficient filling of the great veins and a deficient cardiac return with a decreased cardiac output. There may be obstruction in the pulmonary microcirculation due to a variety of causes including arteriolar spasm and capillary plugging as seen in shock. This not only may cause a decreased return of blood to the vena cavae and a poor cardiac return due to low central venous pressure

* From the Division of Surgery, Walter Reed Army Institute of Research, Washington, D. C.

but, by obstructing the pulmonary microcirculation, result in acute cor pulmonale and a deficiency in venous return to the left heart (fig. 1).[1] There may be damage to the heart itself due to poor perfusion from a low arterial pressure or to a wide variety of conditions such as coronary insufficiency, valvular disease, gross or micro-infarction, tamponade or other cardiac conditions. This alone can result in thrombophlebitis.[2] Any or all of these can result in a decrease in cardiac output which results in a decrease in blood flow with or without a decrease in arterial blood pressure. Whether or not there is a decreased blood pressure will depend on the balance between cardiac output on one hand and peripheral resistance on the other.

Arteriolar constriction pinches off flow through the arteriole. This commonly occurs in shock (fig. 2). In general, if there is for any reason a decrease in cardiac output with a consequent tendency toward a low arterial pressure, there will be the release of catecholamines with peripheral vasoconstriction in an attempt to maintain arterial blood pressure at a normal level. In addition to endogenous catecholamines there may be other reasons for vasoconstriction. The vasoconstriction, particularly if accompanied by a decrease in arterial pressure, will enable only a small flow through the arteriole. This deficient flow is of course reflected in a lessened flow in the capillaries, with an increase in the capillary transit time and venous acidosis (fig. 3). Slow capillary flow results in a slow venous flow. The relaxation of arteriolar vasoconstriction by a vasodilator, in the presence of a reasonably adequate blood volume, causes an increase in capillary flow which very quickly washes out capillary and venous lactic acid, reversing the trend toward acidosis (fig. 3) and also the

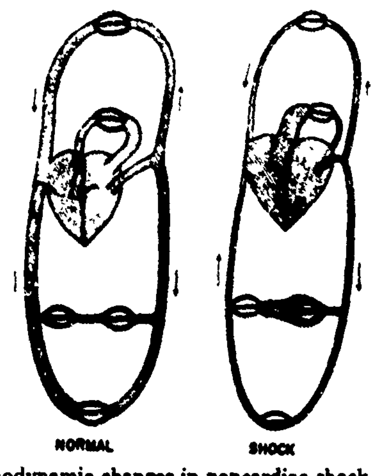


FIG. 1. Diagram of hemodynamic changes in noncardiac shock. On the *left* is the normal situation. The width of the vessels corresponds roughly to their actual diameter and blood flow. In shock, there is relative obstruction in the lungs, liver and peripheral small vessels. This causes a damming back of blood with decreased vena caval and pulmonary vein filling. This, in turn, causes a decreased return to both the left and right heart. A decreased cardiac output and low systemic arterial pressure result.

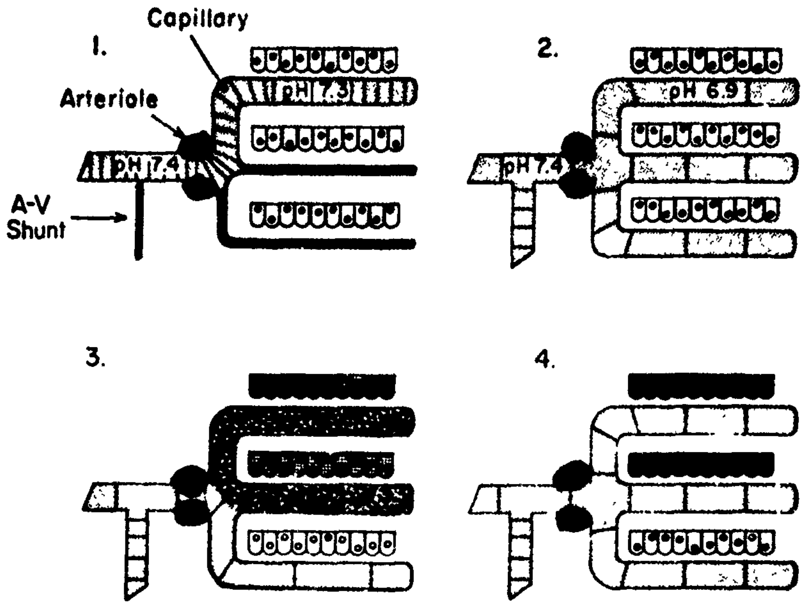


FIG. 2. Mechanism of traumatic shock. *1*, normal condition. Arteriole is open. Arteriovenous shunt is closed. Only one capillary is being perfused while the others rest. Capillaries open on demand of the cells adjacent to them. Constant perfusion is not necessary. Blood flow through the capillary is rapid. Arterial pH, 7.4. Venous pH, 7.3. *2*, early shock. There is arterial hypotension. Arteriole is constricted, letting less blood through. Arteriovenous shunt has opened. All capillaries have opened on demand of their cells. As a result of these changes capillary blood flow is extremely sluggish. More lactic acid has time to accumulate in capillary blood, producing pH of 6.9 in the venous end of the capillary. *3*, arteriole remains constricted and arteriovenous shunt remains open. The sluggish and acid blood in two of the capillaries has been clotted by action of red cell thromboplastin. This has stopped perfusion in these capillaries completely. Cells adjacent to these two capillaries are dying. *4*, irreversible shock. Capillary clots have been lysed by endogenous fibrinolysin and capillary flow restored. However, cells supplied by the formerly clotted capillaries are now dead.

hypercoagulability secondary to the acidosis.[4] Not only will catecholamines and vasoconstriction encourage stasis and coagulation, but stasis and coagulation may promote vasospasm. The vasoconstriction of "milk leg" is well known. This may occur through at least two mechanisms. (1) Platelet thrombi may break up, yielding serotonin which stimulates contraction of vascular smooth muscle. (2) When fibrinogen is split by the proteolytic enzyme thrombin, the first thing that happens is the splitting off of two peptides, "A" and "B." These peptides are strongly stimulatory to smooth muscle and are produced in sufficient concentration to cause vasospasm of whatever vessel is being clotted.[8] Thus a vicious circle is produced. Vasospasm encourages thrombosis. Thrombosis encourages vasospasm.

Arterial blood pressure is determined by the previous factors. A wound may create a hole in the arterial tree and lower pressure directly.

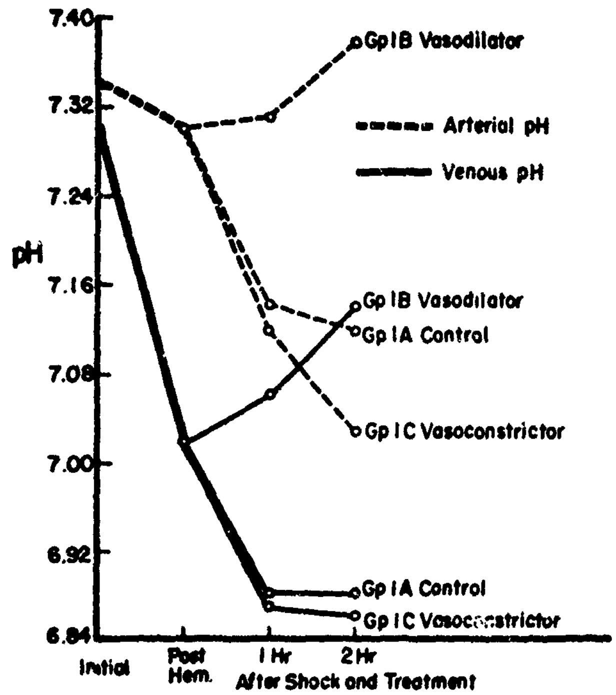


FIG. 3. Arterial and venous pH's taken before and after hemorrhage in dogs and at 1- and 2-hr intervals following hemorrhage during hypotension at 40 mm Hg. Note that during hemorrhage the arterial pH dropped only slightly while the venous pH dropped significantly more ($p < 0.05$). All animals received the same treatment up until this point. After completion of hemorrhage, note that the control group pH dropped significantly in both arterial and venous blood. The group treated with a vasoconstrictor dropped even more. However, the vasodilator-treated dogs showed an improvement in both arterial and venous pH. In fact, the arterial pH actually exceeded initial values. Differences between vasodilated animals and controls were highly significant ($p < 0.001$). The large arterio-venous difference after hemorrhage reflects slow capillary flow.

Capillary dilation. When there is poor cardiac output, vasoconstriction and open arteriovenous shunts, little blood is left to enter the capillaries. Normally, only a few (20 per cent) capillaries are open at any one time (see fig. 2). The flow through that capillary is good and cells serviced by that capillary are soon satisfied with their state of oxygenation and nutrition. When this is satisfactory, mast cells which lie adjacent to the capillary stop secreting histamine and that capillary closes. Meanwhile, another group of cells near another capillary begins to feel the need of capillary perfusion, mast cells along that capillary secrete histamine and that capillary opens, so that various capillaries take turns being perfused.[63, 64] However, under conditions described above, capillary flow is diminished. The capillary being perfused may be perfused so poorly that the cells nourished by it are not yet satisfied when another group of cells feels the need of perfusion and two capillaries then are open. This process may extend till all capillaries are open. Then the difficulty is com-

pounded with less blood flow through the arteriole to supply many capillaries. Capillary flow thus becomes profoundly stagnant. This stagnation not only affects coagulability but brings on an immediate acidosis due to the addition of normal quantities of lactic acid and acid metabolites to the slow flowing blood. The flow may be so poor that aerobic metabolism is replaced by anaerobic metabolism, which results in increased amounts of lactic acid. Acidosis causes an increased coagulability (see below). In addition, the great veins are not filled fast enough, central venous pressure declines and cardiac output falls. The slow filling of the veins causes slow flow in the veins which predisposes to venous thrombosis.

Viscosity of blood. Blood, unlike water, is not a Newtonian fluid; its viscosity varies with its speed of flow. The faster it flows the less the viscosity, the slower it flows the greater its viscosity. The cause of this is not known but may be related to red cell attraction. In addition, viscosity varies with the hematocrit; the higher the hematocrit, the greater the viscosity. A high hematocrit, while enabling a higher oxygen carrying capacity, may actually lessen capillary perfusion by increasing viscosity. This fact is utilized by some surgeons by diluting blood with dextran or other suitable fluid to prime extracorporeal circulation apparatus preparatory to open heart surgery to promote flow, finding that this is preferable to using whole blood for priming. It has been found by Peruvian surgeons doing open heart surgery on patients with high hematocrits due to living at a high altitude, that bleeding the patient before surgery to a normal hematocrit will prevent hemorrhagic complications which are due to disseminated intravascular coagulation.[1]

FACTORS RELATED TO HYPERCOAGULABILITY

Hypercoagulability is difficult to measure or prove. There is no satisfactory laboratory test for it. However, there is considerable evidence for its existence. One easily done test is the usual Lee-White clotting time carried out in siliconized tubes. If this is done the normal clotting time in humans is about 30 min. A properly performed test is abnormal if below 15 min. There is thus a great deal of time to note acceleration of clotting time. The causes of hypercoagulability are unknown; however, there is some evidence for several mechanisms for its production.

Acidosis. Extreme acidosis may be quickly produced under the circumstances of slow capillary flow as typified by shock (fig. 3). While normal quantities of lactic acid and other acid metabolites are being thrown into capillary blood, the concentration of these products in the blood increases, because less blood passes in any given moment. This rapidly produces a metabolic acidosis in the blood by the time it finally reaches the venous end of the capillary. In addition, as the cells become more anoxic due to the slow blood flow, not enough oxygen is available for complete metabolism, and anoxic metabolism results, with an increased production of lactic acid and a compounding of the acidosis. The pH is then particularly low in the veins. The

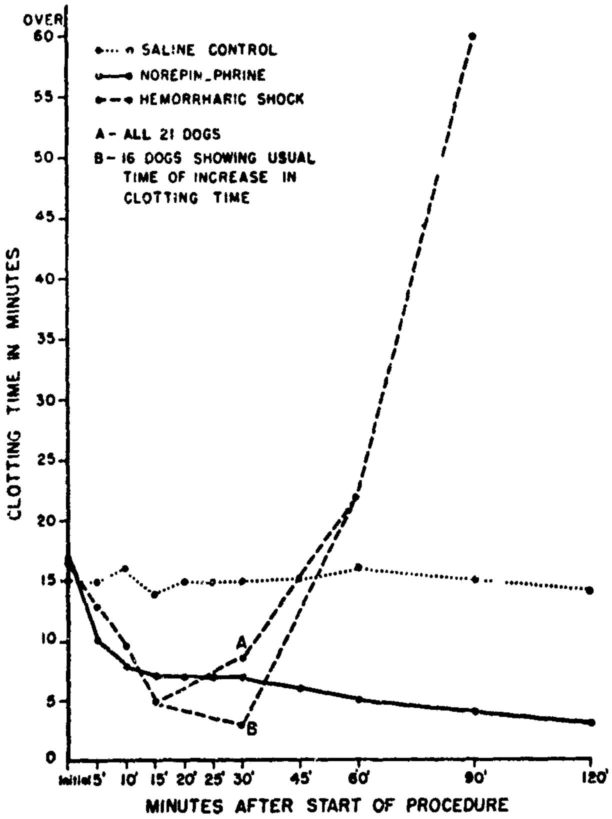


FIG. 4. Average Lee-White clotting times (using siliconized tubes) in dogs subjected to norepinephrine drip and to shock. Note that the clotting times on the normal saline control animals showed no significant changes during the 2-hr period. Both dogs subjected to hemorrhagic shock and dogs given norepinephrine in saline infusion showed a significant decrease in clotting times. The differences between the latter two groups are not significant over the first 30 min. However, after 30 min. the dogs subjected to norepinephrine showed a continuing marked decrease in clotting time, whereas the dogs subjected to hemorrhagic shock showed a rapid increase to incoagulability due to disseminated intravascular coagulation.

lactic acid generates in the capillary blood but is evident by laboratory test first in the veins (fig. 3). There is a widening of the arteriovenous pH difference due to the greater fall of pH in the veins. As shock progresses, both arterial and venous pH fall (fig. 3), maintaining a wide arteriovenous difference. Acidities of 6.6 have been recorded in the inferior vena cava of dogs in hemorrhagic shock. If a dog is bled approximately half of his blood volume, enough to reduce his blood pressure to 40 mm Hg, it has been found that there is a dramatic shortening of his silicone clotting time coming on within a few minutes (fig. 4).[5] This coincides with the development of the marked acidosis. To check the effect of acidosis on the clotting time of blood, a series of tests were set up in both dogs and humans.[6, 7] It was found that acidosis of below pH

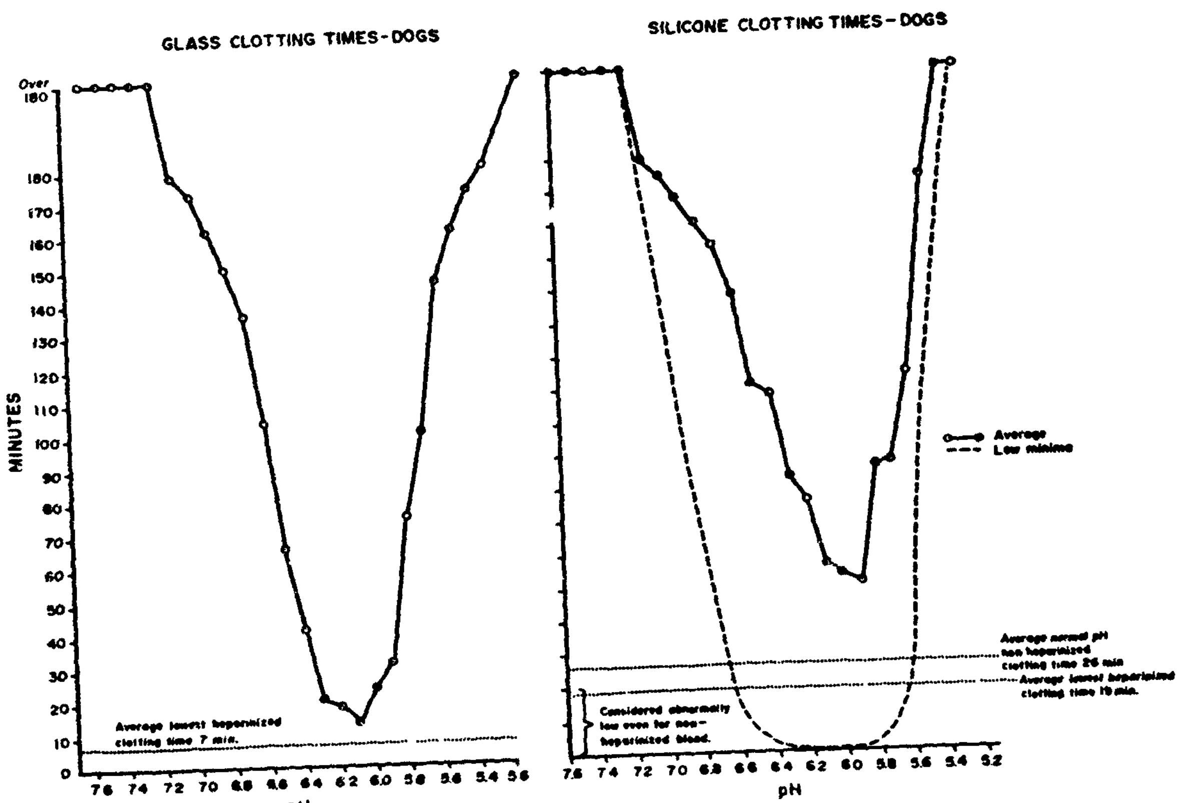


FIG. 5. Glass and silicone clotting times of dogs' blood at different pH's. Average values for each pH do not represent the average shortest clotting time, because some clotting times are on the way up while others are still on their way down. The average lowest clotting time reached at any pH is indicated. The minimal silicone clotting time at each pH is also indicated. Note that the average lowest clotting time of heparinized blood is shorter than average clotting time for nonheparinized blood at normal pH's. Similar shortening takes place in nonheparinized blood, but the initial time is so short that it has less room to fall.

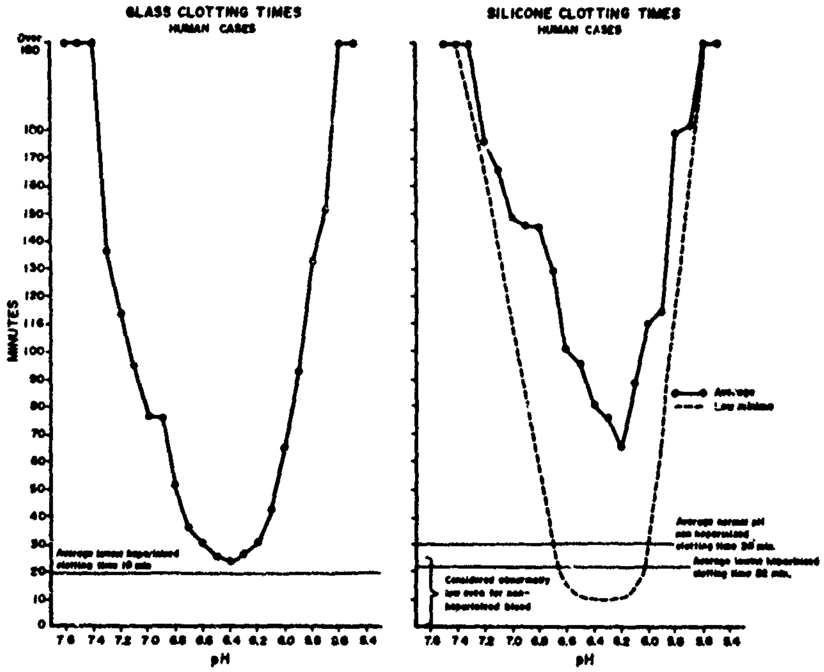


FIG. 6. Glass and silicone clotting times for heparinized human cases at various pH's. Average values for each pH do not represent the average shortest clotting time because some clotting times are on their way up while others are still on their way down. The average lowest clotting times reached at any pH are indicated. The minimal silicone clotting time at each pH is also indicated. Note that the average lowest clotting time of heparinized blood is shorter than average clotting time for nonheparinized blood at normal pH's. Similar shortening takes place in nonheparinized blood.

7.2 affected the clotting time of blood (figs. 5 and 6). Not only was normal blood affected but heparinized blood as well. In fact, when a pH of 6.8 was reached, heparinized blood clotted more quickly than unheparinized blood. Normal unheparinized blood clotted much more quickly than normal, either in glass or siliconized tubes. Prothrombin consumption was also much greater in this blood. It is evident from this work that heparin is inactivated in the presence of acidosis. It is conceivable that there is a normal level of circulating endogenous heparin which helps regulate coagulation and keeps the blood fluid. Acidosis may inactivate this normally circulating heparin as a possible mechanism for reducing clotting time and producing a hypercoagulability.

A similar decrease in clotting time in dogs may be brought on by an intravenous drip of norepinephrine (fig. 4).[8] Epinephrine and norepinephrine are at high levels in the blood in shocked animals after hemorrhage and during shock. They can produce hypercoagulability by inducing acidosis by vasoconstriction and decreased capillary flow as described above.

That acidosis contributes to intravascular coagulation, and that by correcting the acidosis coagulation can be prevented, is documented by a recent

study.[9] Dogs in severe acidosis had intravascular coagulation as shown by such coagulation changes as depletion of clotting factors and prolongation of silicone clotting time and partial thromboplastin time. All these changes could be significantly prevented by treatment with tromethamine and sodium bicarbonate (figs. 7 and 8).[9]

High levels of clotting factors. It has been said that the high levels of clotting factors associated with pregnancy cause a hypercoagulable state.[10] A high level of factor VIII has been associated with hypercoagulability.[11] There is evidence that the higher the level of fibrinogen in dogs, the more the level will fall when thrombin is injected (fig. 9).[12] High levels of fibrinogen are associated with a high sedimentation rate and an increased tendency of red cells to stick together. High levels of fibrinogen are associated with an increase in blood viscosity and an increased tendency for rouleau formation.[13] The manufacture or release of fibrinogen is one of the most rapid and remarkable processes in the body. Any stress such as injury, shock or mental stress results in the rapid increase in level of blood fibrinogen. This may reach the speed of 50 mg per cent per hr (fig. 10).[14, 15] This may be stimulated through the

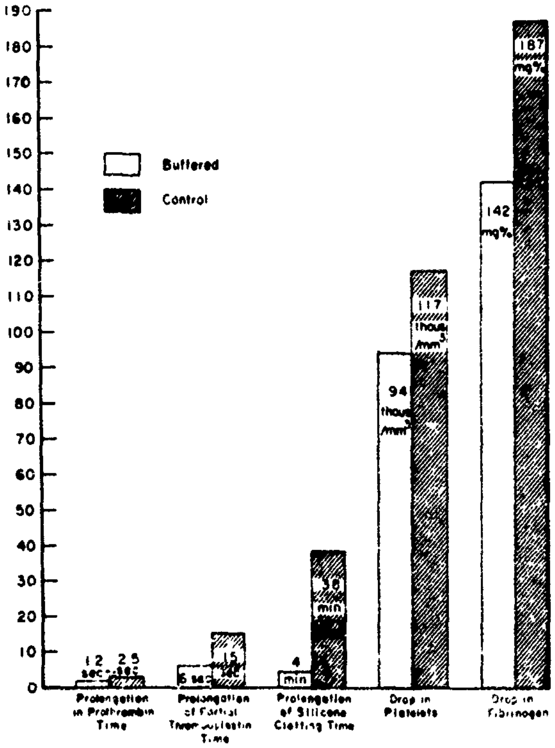


FIG. 7. A comparison of the average change between buffered and nonbuffered dogs after 4 hr of shock in several clotting parameters shows that in each case a severe degree of change occurred in the nonbuffered group. Buffering of the blood with THAM and $NaHCO_3$ prevents the changes due to intravascular coagulation.

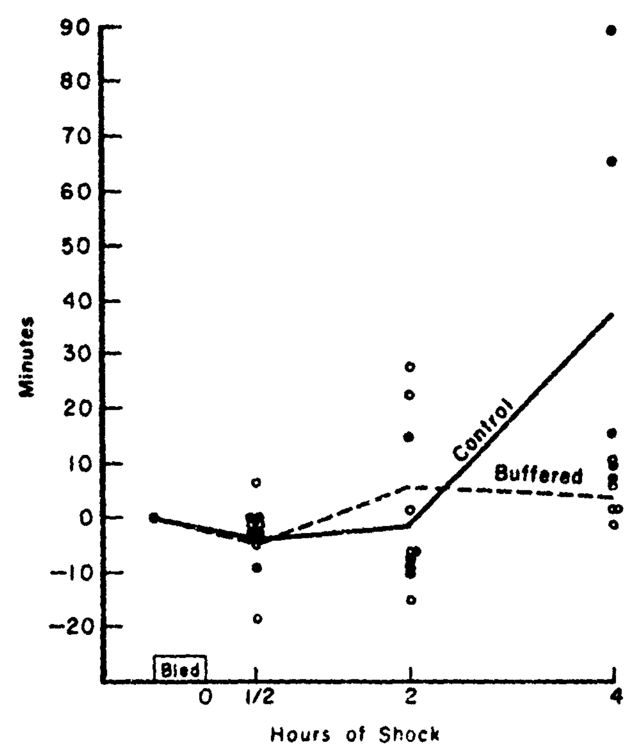


FIG. 8. Buffered and nonbuffered dogs are compared in terms of the average changes in partial thromboplastin time. Buffering of blood with THAM and $NaHCO_3$ prevents the prolongation of silicone clotting time due to intravascular coagulation.

corticosteroid mechanism (fig. 11). However, the mere presence of a low fibrinogen level is also a powerful stimulus. It is probable that other clotting factors participate in this increase. Fibrinogen levels may rise quickly from 200 mg per cent to 800 mg per cent or more. This has a tremendous effect on red cell aggregation, rouleau formation, blood viscosity[13] and coagulability of the blood.[12] It is well-known that blood cortisone levels are high in late pregnancy. Cortisone administration is associated with a high blood fibrinogen level.[14, 62] Apparently the higher the fibrinogen level, the more susceptible the blood is to an intravascular clotting episode, perhaps because there is more fibrinogen available to form clots.[12] Pregnancy not only is associated with a high fibrinogen level but a high level of other clotting factors as well.[10] There is an average increase of 146 per cent in factor VIII and a 138 per cent increase in factor IX.[16] There is accelerated thromboplastin generation. Prothrombin time is shortened. In addition to the high level of clotting factors contributing to a hypercoagulable state, platelets also become more sticky. This occurs only to a limited degree in normal pregnancy, but, in the case of toxemia, the platelet adhesiveness becomes very marked.[17] Venous thrombosis

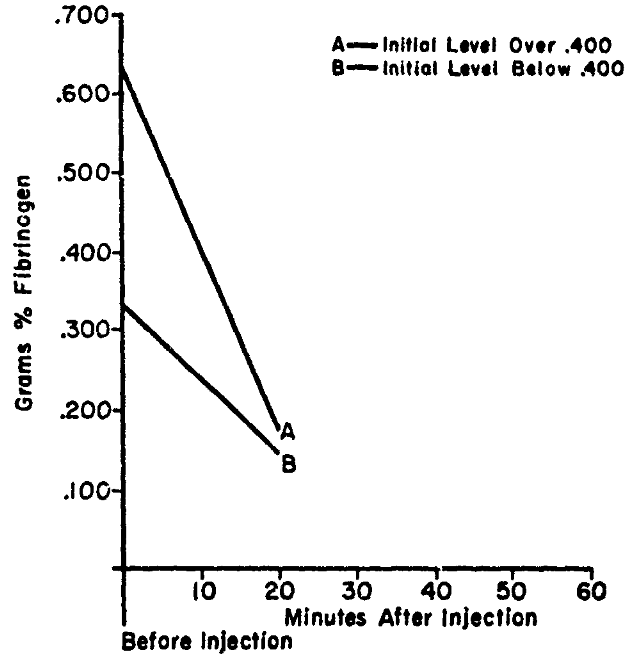


FIG. 9. Fibrinogen drop in dogs given an intravascular injection of thrombin. Dogs having an initial fibrinogen level of 400 mg per cent or over are compared with those having an initial level of less than 400 mg per cent. The former had a much greater drop than the latter

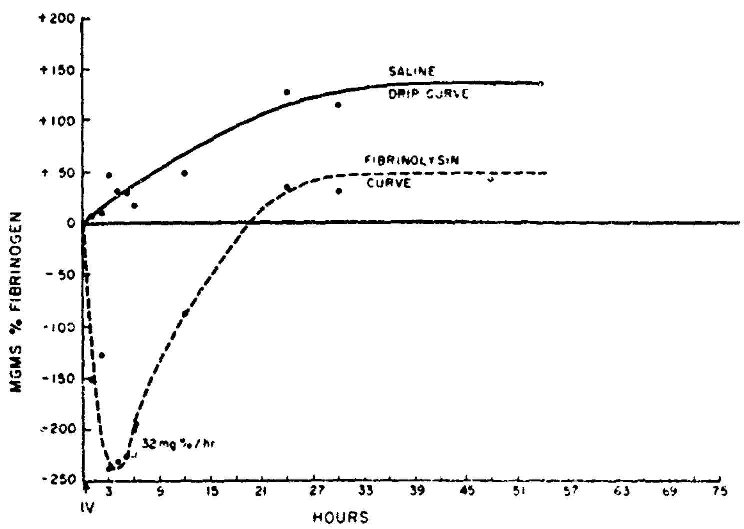


FIG. 10. Fibrinogen levels in dogs. In those dogs sedated and given a saline drip there is a significant increase of fibrinogen amounting to 135 mg per cent. This is presumed to be the result of the stress of surgery and being confined to the operating table for 7 hr. In those dogs subjected to the same procedure but having fibrinolysin in the saline drip there is an immediate dramatic fall in fibrinogen levels amounting to 238 mg per cent within 3 hr. After this began a dramatic increase in fibrinogen amounting to 285 mg per cent or to 32 mg per cent per hr at the steep part of the curve. This rise continued to supranormal levels and continued to rise for 30 hr.

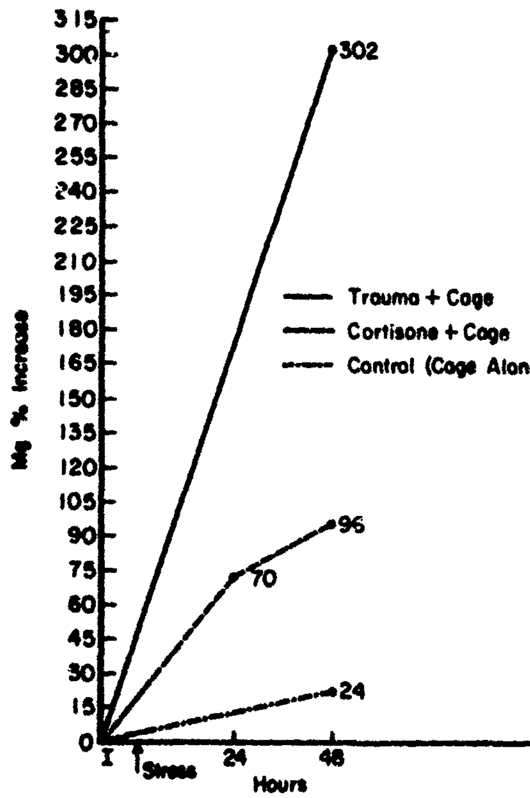


FIG. 11. Milligrams per cent of increase in fibrinogen following three types of stress in dogs. All three groups were confined to cages. The group designated by the *solid line* had trauma to one thigh after the initial reading. The group designated by the *dashed line* had cortisone administered after the initial reading. All groups showed a significant increase over their initial level and over the increase of the control group.

is a common complication in the term pregnant and *post partum* patient. It is particularly lethal and was the most common source of fatal pulmonary embolism in surveys of U. S. Army Hospitals at Frankfurt, Germany, and Fort Belevoir, Virginia.[1]

The stickiness or adhesiveness of platelets is known to vary considerably. Normally platelets keep fairly separate from each other (fig. 12). Under certain conditions such as shock[1] and toxemia of pregnancy,[17] the adhesiveness increases, platelets tend to clump, adhering to each other whenever they touch each other (fig. 13). Endotoxins and exotoxins are substances which cause platelet stickiness and clumping, with consequent dramatic changes manifested by a sudden disappearance of circulating platelets and formation of platelet thrombi throughout the microcirculation (figs. 14 to 16). There is immediate incoagulability of circulating blood due to clotting factor depletion. With platelet breakdown, thromboplastin is liberated with initiates coagulation (figs. 17 to 21).

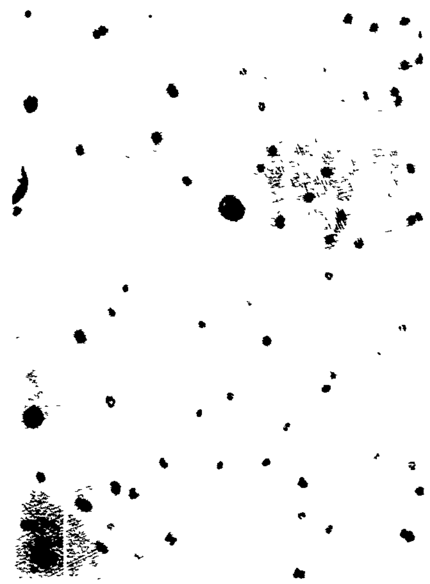


FIG. 12. Platelets in a counting chamber from a sample of blood taken from a normal dog Note scattering of numerous individual platelets.

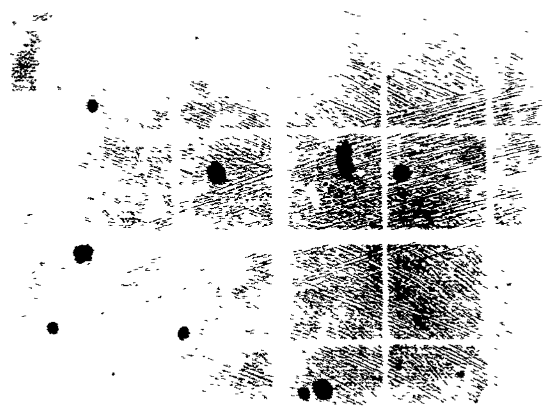


FIG. 13 Platelets in a counting chamber from a sample of blood taken from a dog in shock. Note clumping of the relatively few platelets.

The adhesiveness of platelets can be increased by many endogenous factors. For instance, placental trophoblast may cause it. Platelet stickiness is moderately increased in pregnancy, but is markedly increased in pre-eclampsia and toxemia.[17]

Adrenomedullary hormones. Norepinephrine administration decreases the silicone clotting time in dogs (fig. 4). Teleologically this is understandable; a wounded animal would need to clot his blood faster to help stop hemorrhage.

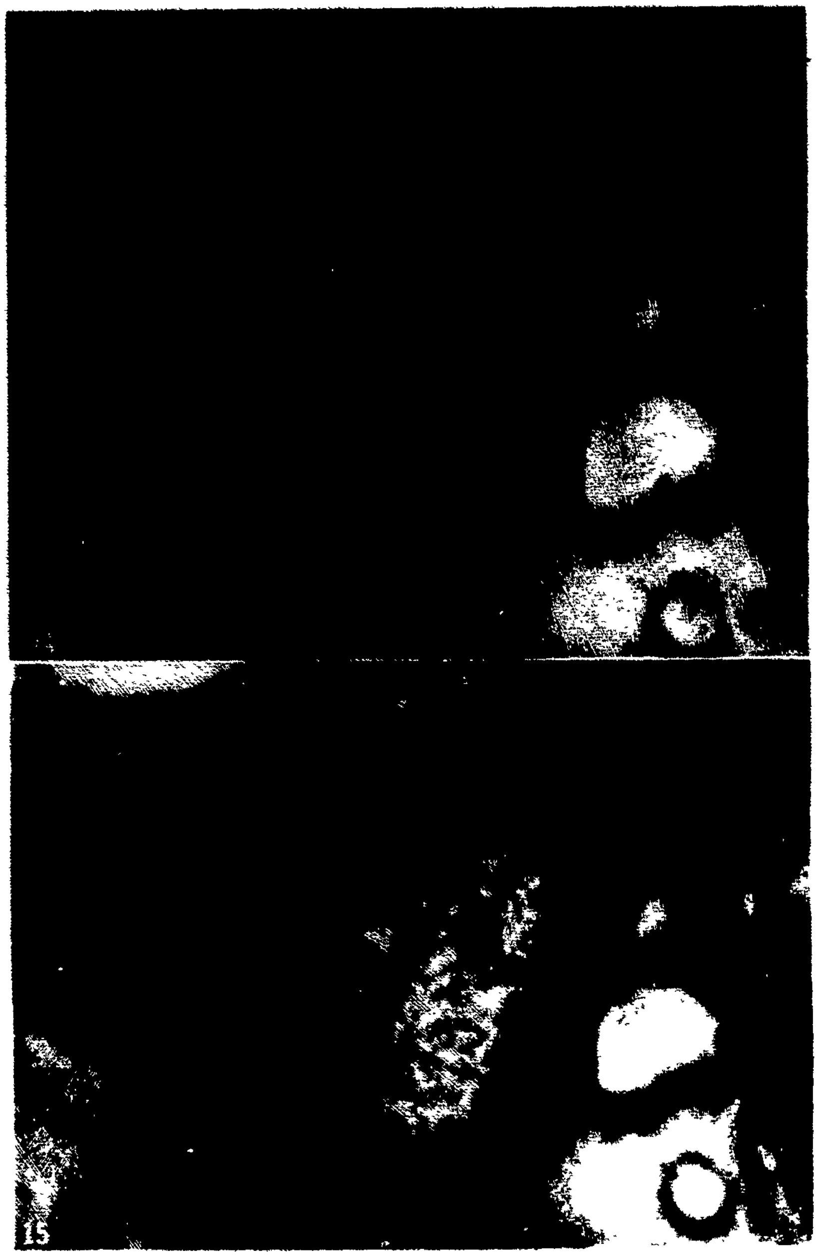


FIG. 14 (*upper*). Bifurcation of pulmonary arteriole prior to injection of bacterial toxin. Taken by strobe illumination from rabbit's ear.

FIG. 15 (*lower*). Bifurcation of the pulmonary arteriole shown in figure 14 after one branch has been blocked by platelet thrombus secondary to intravenous injection of coagulase positive staphylococci. Coagulation may occur above and below a block. Taken by strobe illumination from rabbit's ear.

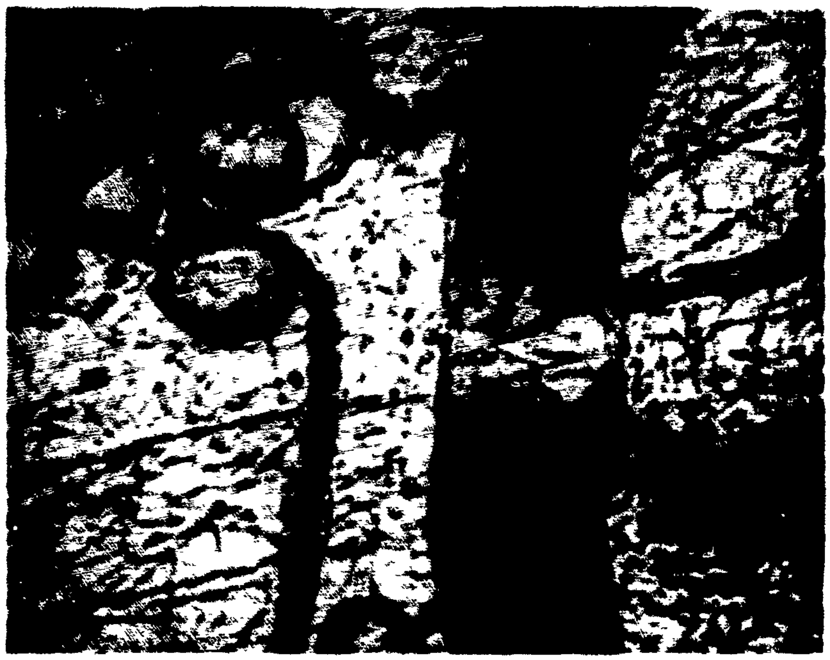


FIG. 16. A platelet embolus lodged in microvessel of rabbit's ear formed as a result of intravenous injection of coagulase positive staphylococci.

The mechanism of action is unknown but may be through the production of venous acidosis, as described above.

Adrenocortical hormones. These substances caused a marked elevation in fibrinogen (fig. 11). Fibrinogen is known to be elevated in pregnancy, as are other factors such as II, VII and X. The reason for this is not definitely known but may well be related to the stress and high level of adrenocorticoids which are present in pregnancy. The blood of pregnant women seems to clot easily and episodes of large vessel thrombosis are common. The Shwartzman reaction (a syndrome caused by disseminated intravascular coagulation) can be induced in pregnant rabbits with only one injection of bacterial endotoxin, whereas two injections are otherwise necessary. Stress of injury, mental stress or shock produces an elevation of blood fibrinogen.[14] It is these same states in which are found a decreased silicone clotting time and which are characterized by an increase in both adrenomedullary and adrenocortical hormones.

Stimulation of the splanchnic nerves may increase the coagulability of blood.[18] This may occur during abdominal surgery. If the adrenal gland is removed on one side, splanchnic stimulation on that side does not shorten the clotting time, whereas splanchnic stimulation on the other side is still effective. The clotting factor must therefore be due to adrenal discharge. Since stimulation of the nerves supplying the liver and intestines does not hasten clotting and since an increase in adrenalin has no effect in the absence of the liver and

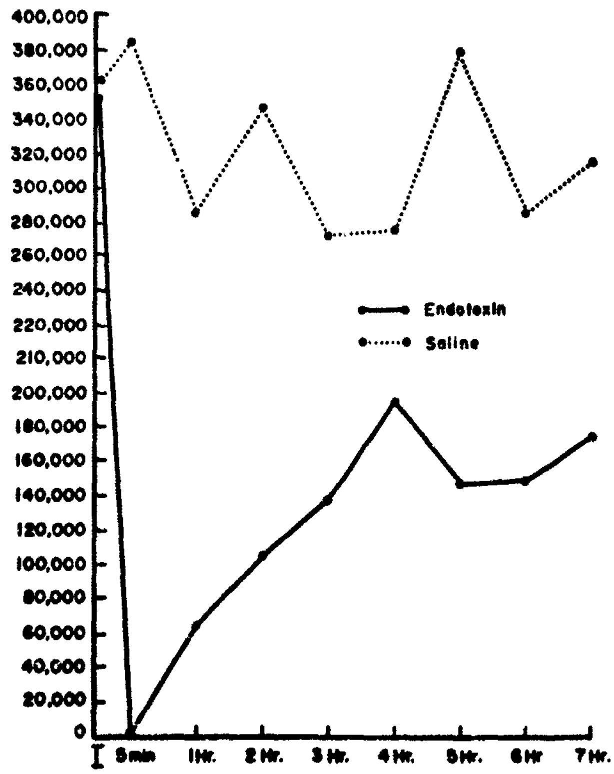


FIG. 17. Average platelet counts in dogs. Endotoxin was injected immediately after initial reading. Note that there was an immediate disappearance in platelets after endotoxin with a gradual partial recovery. However, platelets remained significantly depressed for the entire 7-hr period. There was no statistical change in the platelets of dogs injected with saline.

intestines, the shortening of the clotting time after splanchnic stimulation may be accounted for by the action of adrenal discharges on the liver (elevation of fibrinogen level?). Closely related to the above is the hastening of coagulation in pain and emotional excitement.[19] The effect of splanchnic stimulation may be mediated through decrease in capillary blood flow with vasoconstriction and production of acidosis secondary to slow capillary flow.

SUBSTANCES WHICH MAY INITIATE COAGULATION

Many substances, when introduced into the bloodstream, may, under certain circumstances, initiate coagulation. In the presence of a normal blood flow, no clot may result, because coagulation is slow and clot dissolution may be speeded up. However, in the presence of a low flow state, massive coagulation may occur. Some of these substances which may initiate coagulation are: red cell thromboplastin as liberated by hemolysis, bacterial toxins (endotoxin and exotoxin), particulate matter (amniotic fluid or large molecular dextran),

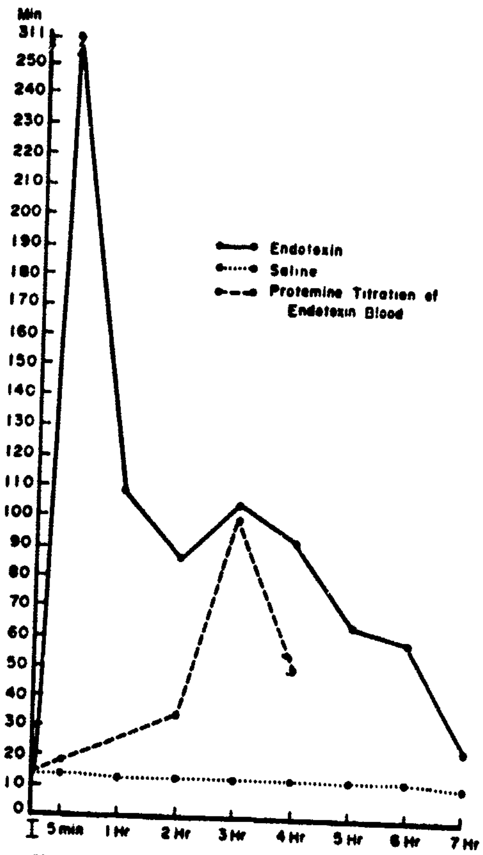


FIG. 18. Average Lee-White clotting times (in siliconized tubes) of dogs. Endotoxin was administered just after the initial reading. Note that there was a dramatic prolongation of clotting times from a preinjection average of 12 min to 311 min, 5 min after injection of endotoxin. Note also that the clotting time did not return to statistically normal levels until 7 hr after injection. This is in contrast to the glass clotting times. Dogs injected with saline showed no change in clotting time.

platelet agglutination, tissue or tissue juices from the placenta, malignant tumors, antigen-antibody complexes, ischemia, fibrinolysis inhibition, fats and fatty acids or a high fat diet and activation of Hageman factor XII by surfaces.

Hemolysis. One of the most interesting and dramatic of these is the thromboplastin normally located within the red cell but liberated by hemolysis. It was first described by Quick[20] in 1954, but very little attention has been paid to it. Ordinarily it has no effect, because it remains within the red cell. It is separable from hemoglobin and is associated with a fat soluble fraction.[21] It may or may not be identical to factor R of Hellem.[22] Factor R turned out to be adenosine diphosphate (ADP) and is a potent platelet agglutinator.[23] As we

FIG. 19. Average fibrinogen levels in dogs injected with endotoxin at point of *arrow E*. Note a progressive fall in fibrinogen from a preinjection level of 237 mg per cent to 155 mg per cent after 6 hr. There was no significant change in fibrinogen levels of the paired animals which were preheparinized.

have seen, platelet agglutination and viscous metamorphosis causes fibrin formation.

The factor in the red cell, whatever it is, has no significance under normal flow states. Even if it is liberated by red cell hemolysis it has no particular clinical effect under ordinary conditions. For instance, a normal man may be given a liter of distilled water intravenously with a dramatic hemolysis of his red cells but no clinical effect.[24] There is only transient hemoglobinemia and hemoglobinuria. One hundred milliliters of blood may be removed from a dog, frozen, thawed and returned to the animal with no apparent clinical effect.[21] However, if certain tests are performed on the animal's blood, it is evident that changes have taken place. The changes are remarkably similar to those seen after the intravenous injection of thrombin. The blood immediately becomes incoagulable in siliconized tubes (fig. 22). This is due to the consumption of clotting factors by intravascular clotting to such an extent that the remaining blood is left deficient in clotting factors and thus incoagulable. In fact the onset of widespread intravascular coagulation is always heralded by a clotting defect.[1] Prothrombin time is prolonged (fig. 23). There is a significant decrease in fibrinogen and other clotting factors (fig. 24). However, all of these

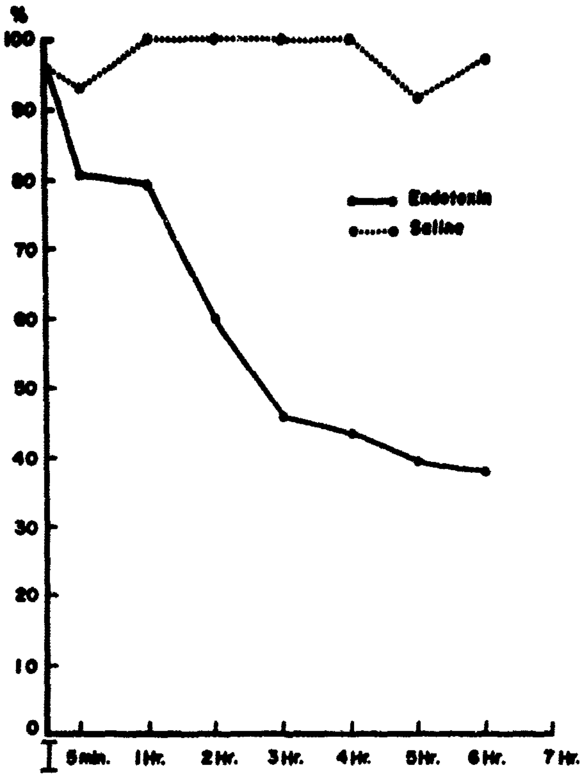


FIG 10. Average determinations of factor V in dogs. Endotoxin was injected immediately after initial reading. Note a progressive fall in factor V from a preinjection level of 96 per cent of normal to 38 per cent of normal 6 hr later. There was no statistical change in the dogs injected with saline.

changes return to normal within 4 hr in the normal animal. It is evident that intravascular coagulation has taken place, but the normal animal was able to take care of it because of his normal blood flow. However, if the blood flow is diminished as in shock, the results are completely different.[21] In this case only 20 ml of autologous hemolyzed blood produces fatal intravascular coagulation in an animal in otherwise nonlethal shock. It is evident that while hemolysis is relatively harmless in a normal circulation, it results in widespread coagulation with accumulation of fibrin when it is superimposed on a state of slow blood flow as is present in shock and many other states.

It is well-known that trauma, particularly a crushing injury, in some way predisposes to thrombophlebitis. Although several mechanisms may be in action, hemolysis may be one of them. It has been shown[21] that trauma or a crushing injury results in an increasing level of hemolysis, reaching a maximum about 48 hr after injury. The hemoglobin level of the blood actually increases during this relatively long time in the face of normal kidney function

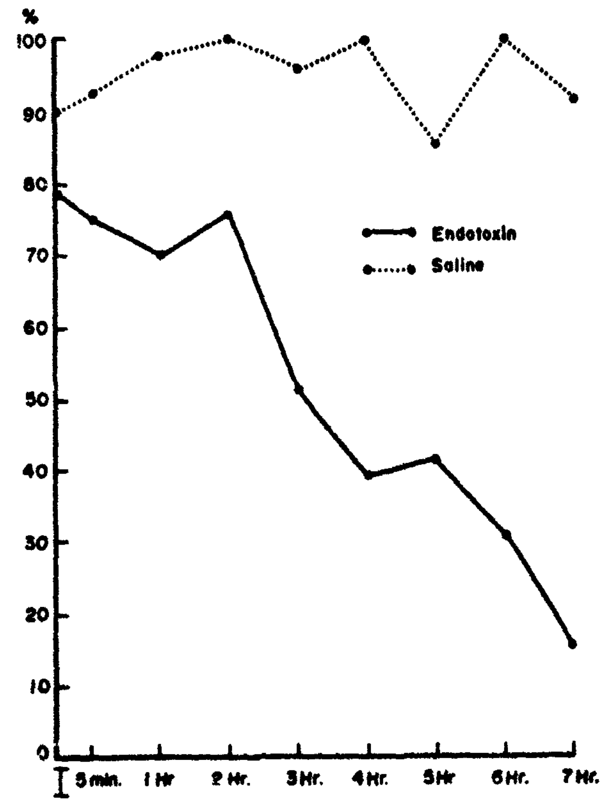


FIG. 21. Average determinations of factor VII in dogs. Endotoxin was injected immediately after initial readings. Note a progressive fall in factor VII from a preinjection level of 78 per cent of normal to 16 per cent of normal at the end of 7 hr. Factor VII did not change statistically in the saline injected dogs.

(fig. 25). Hemolysis of this degree would normally be nearly completely removed by the kidneys within 4 hr (fig. 26). The mechanism of this increase of hemolysis in the blood is unknown but may be in part merely the absorption of ecchymoses and hematoma, or there may be some specific hemolysin present. This hemolysis of red cells under ordinary circumstances would cause no problem, but in the presence of shock which may accompany the trauma, this amount of hemolysis becomes a potent factor in causing intravascular coagulation.[21] Blood which is slow-moving, acidotic and hypercoagulable is susceptible to intravascular coagulation by red cell thromboplastin liberated by this modest amount of hemolysis. Of course, the trauma or crushing injury may act also by other mechanisms such as widespread injury to vessels and their endothelium, partial or complete mechanical blockage of blood flow, the entrance of tissue thromboplastin into the circulation, necrosis of tissue either directly or by damage to the circulation, the causation of shock (and

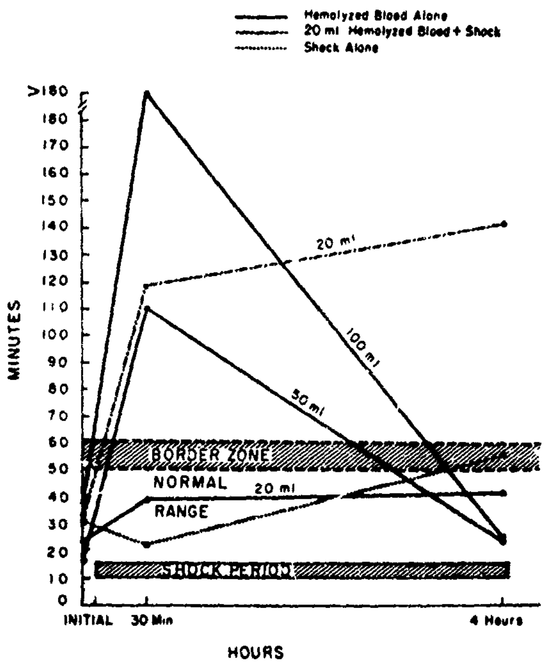


FIG. 22. Silicone clotting times of some groups of dogs. Dogs subjected to shock alone show a decrease in silicone clotting time as a result of hemorrhage with a subsequent lengthening of time at the end of the shock period into a border zone of 55 min. Three groups of dogs given hemolyzed blood without any shock procedure show varying changes according to their dosage of hemolyzed blood but all ended up within the normal range after 4 hr. Dogs given 50 and 100 ml of hemolyzed blood showed a transient but dramatic elevation in silicone clotting times at 30 min after administration of the hemolyzed blood. In dogs given 100 ml the 30-min samples frequently did not clot for as long as a week. Dogs subjected to hemorrhagic shock after administration of 20 cc of hemolyzed blood showed the immediate lengthening of clotting time characteristic of the other dogs given 50 or 100 ml of hemolyzed blood, but instead of returning to normal levels within 4 hr showed a further increase in clotting time. This prolonged clotting time at the end of shock is characteristic of irreversibility. The initial characteristic shortening of the clotting time immediately after hemorrhage without hemolyzed blood is converted to a marked lengthening by the 20 ml of hemolyzed blood.

slow capillary perfusion) by blood loss with its systemic effects of acidosis and other effects described in this paper.

Bacterial Toxins. A second type of endogenous factor which may initiate coagulation is bacterial toxin. Filtrates from pathogenic strains of *Staphylococcus aureus* (exotoxins) have been known since 1903 to be capable of coagulating blood.[25] Filtrates of pathogenic staphylococci (coagulase positive) are capable of causing platelet agglutination with platelet thrombi formation (figs. 14 to 16) and of clotting fibrinogen. They are in this sense similar in action to thrombin. However, unlike thrombin, these filtrates act even in the presence of heparin.[26] Considerable work on this phenomenon has produced the present opinion[27] that staphylocoagulase reacts with prothrombin even in

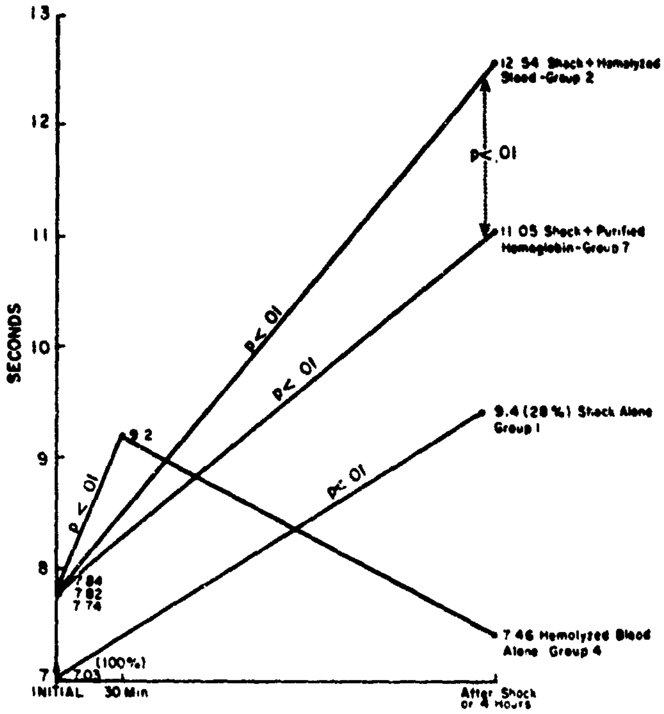


FIG. 23. Prothrombin times of some groups of dogs. The prothrombin times increased significantly in all groups subjected to hemorrhagic shock. The group given 100 ml of hemolysed blood alone without any shock procedure showed a significant increase 30 min following the administration of the blood. However, it had returned to normal levels at the end of 4 hr in contrast to those subjected to hemorrhagic shock. Note that there was a significant difference in the prothrombin time increase between those dogs given the whole hemolysed blood (group 2) and those given a purified hemoglobin (group 7). Although the total elevation in both groups was significant, there was significantly less elevation in the purified hemoglobin group.

the absence of calcium and factors V and VII to produce a form of thrombin which is not inhibited by heparin or by the antithrombin of the serum.

The *bacterial endotoxins* of such gram negative organisms as *Bacillus coli, Bacillus proteus, Pseudomonas aeruginosa* and *Serratia marcescens* also produce platelet agglutination and intravascular coagulation. Single lethal doses may not be associated with widespread visible thrombosis. The visible thrombotic effects are typically embodied in the Shwartzman reaction. The two variants of the Shwartzman reaction are the local and generalized varieties, both of which are associated with visible thromboses of small vessels.[26] However, single lethal doses are effective in producing the changes in the clotting mechanism which are characteristic of widespread intravascular coagulation. These include an immediate nearly complete disappearance of circulating platelets (fig. 17), an incoagulability of blood in silicone (fig. 18), a decrease in circulating fibrinogen (fig. 19) and other clotting factors (figs. 20 and 21). The trigger mecha-

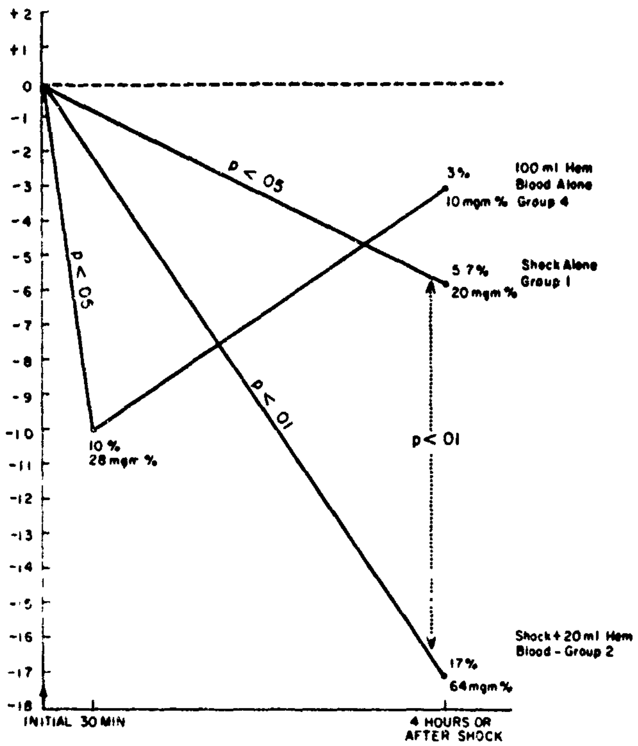


FIG. 24. Fibrinogen levels of dogs subjected to shock, injection of hemolyzed blood, or both. There is a mild but significant fall in fibrinogen in the group subjected to shock alone (group 1). This shock is in most cases reversible. However, there is a much more dramatic fall in fibrinogen in those dogs given hemolyzed blood and subjected to shock (group 2), and which procedure resulted in death in most cases. There is a significant difference in this fall between groups 1 and 2. One hundred milliliters of hemolyzed blood alone without any shock procedure (group 4) resulted in an immediate significant decrease in fibrinogen, but this had returned to normal levels by the end of a 4-hr period. This reflects an immediate conversion of fibrinogen to fibrin by the hemolyzed blood, but the deficiency is quickly made up because no further intravascular clotting was taking place.

nism for this may well be the effect of endotoxin on platelets, causing their agglutination and breakdown. This liberates quantities of thromboplastin in the bloodstream which may initiate coagulation. Endotoxin may also activate factor XII.[29]

Particulate matter such as kaolin (or large molecular dextran) promotes coagulation by the activation of Hageman factor XII.[1] Particulate matter is found in an infinite variety of occasions and may on occasion enter the bloodstream. Amniotic fluid, not thrombogenic in itself, contains a great deal of particulate matter derived from vernix caseosa and meconium. It is this particulate matter which is the active stimulus to clotting.

Platelet agglutination may liberate a thromboplastin. Such substances as endotoxins are particularly attracted to platelets. Ninety-seven per cent of

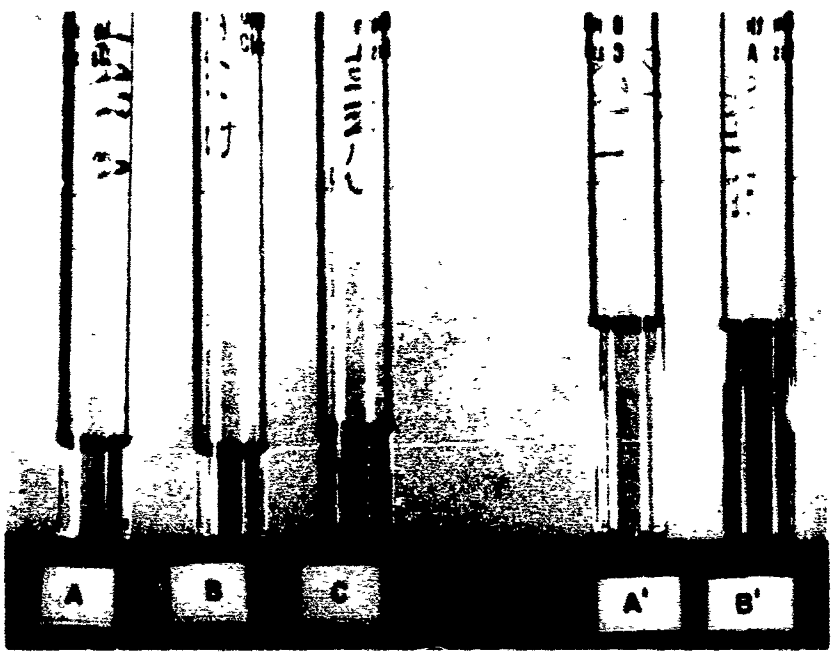


FIG. 25. On the *left* are three blood samples taken from a dog subjected to 100 blows of a padded mallet on one thigh. The first tube was drawn before the trauma, the second tube 30 min following the trauma, and the third tube 48 hr after the trauma. Note that hemolysis which was only mild right after the trauma had increased markedly by the end of 2 days. This is thought to be due to absorption of hematoma and ecchymosis probably via lymphatics. If no hemolyzed blood had been absorbed, the mild hemolysis shown in the second tube would have completely disappeared in a few hours. On the right are two tubes drawn before and after the administration of 20 ml of autogenous blood which had been frozen and thawed. Note that the amount of hemolysis 48 hr after trauma and immediately after the administration of 20 ml of hemolyzed blood is approximately the same.

injected endotoxin in the cellular elements of the blood is located in the platelets. This in some way causes their agglutination. Within a short time the agglutinated platelets begin to fuse and break-down liberating quantities of thromboplastin which, if the platelet thrombi are widespread enough, may be enough to induce clotting. In reverse, platelet agglutination is caused by thrombin with the possibility of a vicious circle.

Tissue or tissue juices from the placenta may also gain access to the bloodstream. These substances may be high in tissue thromboplastin and be potent in producing intravascular coagulation.

Malignant tumors. The increased incidence of thrombophlebitis with malignant disease is well-known. Cells derived from a growing malignant neoplasm may gain access to the bloodstream due to erosion of vessel walls by the tumor or other means. In fact, cancer cells are usually found in the circulating blood of patients with malignant tumors.[30] These cancer cells stimulate coagulation.[1] A layer of fibrin soon covers each cell and promotes its adherence to

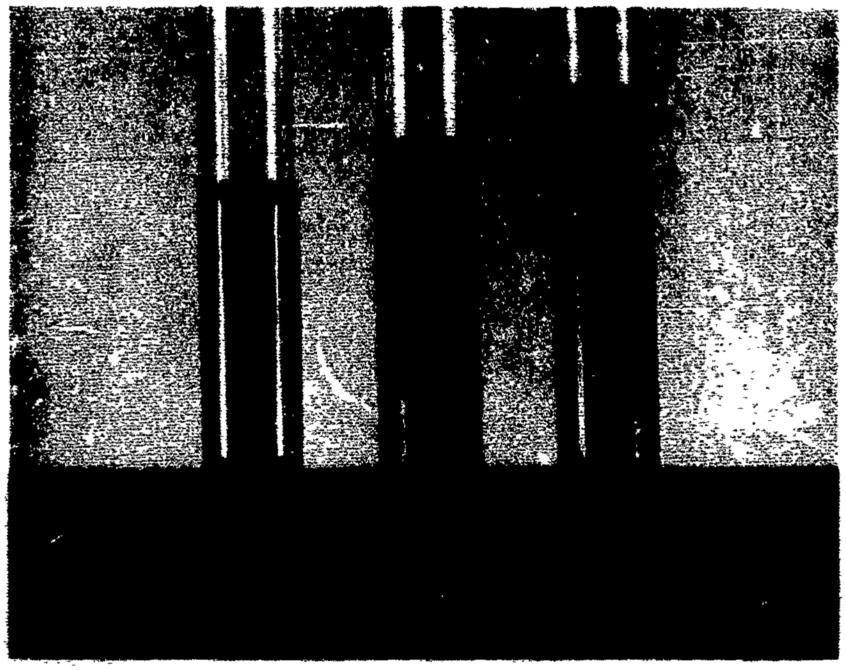


FIG. 26. Three specimens of blood taken from a dog given 20 ml of autogenous hemolyzed blood alone without any shock procedure. The first tube was drawn before administration of hemolyzed blood, the second tube was drawn 30 min after administration of hemolyzed blood, and the third tube 4 hr after administration of hemolyzed blood. Note that there is dramatic clearing of the hemoglobinemia during the 4-hr period. This clearing corresponds to the recovery towards normal of the corresponding changes in fibrinogen, clotting time and endogenous heparin.

capillary endothelium.[31] This results in metastatic growth. This promotes further intravascular coagulation. The effects are similar to injection of tissue thromboplastin. Tissue ischemia also may play a part as may elevated blood steroid and clotting factor levels.

Antigen-antibody complexes. Experiments point to the ability of antigen-antibody complexes to produce intravascular thrombosis.[32] The studies *in vitro* of Robbins and Stetson[33] provide the background for these experiments. Antigen titrations were performed with bovine γ-globulin and bovine serum albumin against rabbit antisera. Supernates and precipitates, formed at equivalence and in zones of antigen or antibody excess, were tested for their coagulation-acceleration activity. Supernates taken from the region of antigen excess produced marked acceleration of clotting when added to normal rabbit blood in silicone. Resuspended specific precipitates and supernates taken at equivalence or in antibody excess were without activity. Soluble antigen-antibody complexes prepared by dissolving specific precipitates in excess antigen showed some activity. Further studies on the role of cellular elements in these reactions demonstrated that the antigen-antibody complexes accelerated

fibrin formation in cell-rich but not in cell-free plasma, which indicates that some component of the buffy coat mediates the effect. In this respect, antigen-antibody complexes mimic the effect of bacterial endotoxin *in vitro*.[34]

In vivo, the thrombotic qualities of antigen-antibody complexes are well demonstrated by the Arthus phenomenon.

In hypersensitive rabbits, intravenous injection of the antigen, after local preparation of the skin with an endotoxin, provokes the local Shwartzman reaction.[35, 36] Antigen-antibody precipitates have been found to be capable of substituting for the provocative intravenous injection of endotoxin in producing the local Shwartzman reaction,[37, 38] which is produced by intravascular coagulation.

In a study of the effects of the intravenous injection of soluble antigen-antibody complexes, McCluskey and colleagues[39] observed that the mice developed a transient glomerulonephritis. Because of its known anti-inflammatory effect, cortisone was given in high doses in order to modify the severity of the glomerulonephritis. The cortisone diminished the severity of the nephritis, but, in addition, in four of five mice that received cortisone and complexes and were killed 1 day later, there was a striking accumulation of amorphous eosinophilic material filling many glomerular capillary loops. This material stained with Weigert's fibrin stain and was blue with Mallory's phosphotungstic acid-hematoxylin. Smaller amounts were found in two of the mice from the same group killed 4 days after treatment, and similar material was found occasionally in small amounts in animals given complexes alone and killed shortly after the last injection. The histology of the glomerular deposits, the known clot promoting effect of soluble antigen-antibody complexes and the known ability of cortisone to "prepare" for the generalized Shwartzman reaction leave little doubt that this reaction was present in these animals.

Thus, although the clot-promoting activity of antigen-antibody complexes has not been studied systematically, experiments to date clearly demonstrate that under certain conditions they are capable of inducing intravascular coagulation *in vivo*.

Ischemia. Although the evidence that ischemia may cause thrombosis is fragmentary, it has long been assumed that it can. A few experiments demonstrate that, at least locally, ischemia can be an etiologic factor.

Nakai and Margaretten[40] studied the pathogenesis of bilateral renal cortical necrosis induced by staphylococcal α-toxin in the rabbit. After 2 hr the glomerular capillaries are dilated and congested, and the precapillary arterioles show a perivascular and medial hemorrhage. After 3 hr necrosis of the renal tubules is obvious, and only after 4 hr do thrombi appear in the venules, precapillary arterioles and a few in the glomerular capillaries. The thrombosis in this instance clearly is secondary to the ischemic necrosis.

A similar sequence of events is to be found in the rabbit experiments of Sheehan and Davis.[41] These authors clamped the renal artery for 3 hr and observed the consequent death of the parenchyma and blood vessels in the

kidney. When the clamp was removed, blood immediately flowed into the arteries and glomeruli, and to a lesser extent into the intertubular capillaries, so that the kidney became congested. This reflow through the kidney was observed to stop about ½ hr later; the phenomenon was referred to as "failed reflow." With the first flow of blood, the dead arteries became dilated, and hemorrhage into the media occurred shortly thereafter. The glomerular capillaries were initially distended with red blood cells. After 2 hr, fibrin appeared along the endothelial surfaces of the arteries and in the glomerular capillaries. Pretreatment with heparin prevented the arterial thrombosis, except in the glomerular capillaries. As in the case of renal necrosis caused by staphylococcal α-toxin, the appearance of the thrombi was secondary to ischemic necrosis of vascular endothelium.

"Increased incidence of thromboembolism associated with malignant disease and the postoperative state apparently is related to accelerated generation of thromboplastin. This accelerating activity is indistinguishable from antihemophilic globulin (factor VIII), which is elevated in patients with cancer or in those undergoing operation. The relationship of thromboembolism to increased antihemophilic globulin is not clear. Accelerated clotting seems to be associated with tissue injury, with or without inflammation. Small localized tumors with little tissue damage do not cause elevated values of antihemophilic globulin, while more extensive lesions or benign diseases accompanied by inflammation usually are associated with increased activity of antihemophilic globulin." [42]

"Data are based on study of 55 patients who underwent surgical treatment, 30 for malignant disease. Hypercoagulability was observed in 22 of the 30. Eight of the 25 patients with nonmalignant conditions showed hypercoagulability; 7 of the 8 had inflammatory lesions. Accelerated thromboplastin generation was found after operation in 25 patients whose preoperative generation of thromboplastin was normal." [42]

Fibrinolysin Inhibition. Fibrinolysis may be inhibited either spontaneously by normally present inhibitors, or artificially by the administration of ϵ-amino caproic acid (EACA). In either case, normally occurring intravascular coagulation or even worse, exaggerated intravascular coagulation, may be tremendously accelerated by denying the natural protective substance to the body. Nilsson[43] reported a 28-year-old man who had thrombosis of veins in both legs followed by hematemesis. Thrombophlebitis progressed to involve subclavian, innominate, pelvic and portal veins. He died after an episode of cerebral thrombosis. At autopsy he had diffuse thrombophlebitis in most major veins, and pulmonary, renal and bone infarcts. Coagulation studies showed the presence of a fibrinolysin inhibitor which inhibited the activation of fibrinolysin by streptokinase or urokinase by 10 to 20 times normal. The inhibitor was present over a 9-month period of observation.

Occasionally when a patient bleeds unusually, a diagnosis of excess spontaneous fibrinolysin ic made and EACA given to combat it. Actually, spon-

taneous fibrinolysin activity is a protective mechanism against an episode of disseminated intravascular coagulation which may be undiagnosed. If EACA is given, the fibrinolysin is inhibited. However, the intravascular coagulation is then free to proceed unimpeded and may progress rapidly to a fatal conclusion. This may be prevented by heparin administered along with the EACA. A number of such cases have been reported.[44-47]

A high fat diet may result in a hypercoagulability[48] and even intravascular coagulation. The mechanism of this is not known but several have been suggested. Fibrinolytic activity may be decreased.[49] Platelet stickiness may be increased.[50] A high fat diet results in the gradual but marked increase in factors II, VII and X of animals fed cow or cocoa butter. Fat injection also results in the decrease of fibrinolytic activity of the blood, thus reducing a protective mechanism against intravascular coagulation. In fact, one of the postulated causes for the Shwartzman reaction is a decrease of fibrinolytic activity.

Activation of Hageman factor XII by surfaces. Closely related to particulate matter and depending on the surface activation (Hageman factor) are changes in the blood produced when the blood is outside the body or contacts foreign material in such cases as extracorporeal circulation in open heart surgery, artificial kidney procedures and the ordinary storage of transfusion blood in various types of containers. Of these, by far the most important is extracorporeal circulation for three reasons: (1) the entire blood volume is repeatedly circulated over foreign surfaces for a period of time; (2) this takes place during surgery when the circulation is in a vasoconstricted, capillary dilated, stagnant state, during which time it is particularly susceptible to coagulation as discussed in the first part of this paper; and (3) a blood-gas interface is usually involved as in disk or bubble oxygenator. Any interface is particularly effective in promoting coagulation[51] due to the influence of surface phenomenon on ionic charges. The reorientation of ionic charges at a surface produces changes which result in the initiation of coagulation.[52] When whole blood is placed in a silicone-treated tube, it clots more slowly (30 min) than when placed in a glass tube (7 min).[53] Exposure of blood to glass or air changes it (activates the surface clotting system) so that even though no visible immediate change occurs in the heparinized blood, when returned to its owner the blood is very toxic and results in death of the animal.[54] Glass, which possesses a negatively charged surface, enhances clotting by converting Hageman factor from its inactive precursor to the activated form.[55] In the identified steps of the intrinsic clotting mechanism, Hageman factor initiates the successive interaction of factors XI, IX, VIII, X and V, which results in the formation of a prothrombin-converting principle or activated proaccelerin which converts prothrombin to thrombin.[56, 57] Blood which has been exposed to glass then, even though heparinized, has had its Hageman factor XII activated. It may then clot when the heparin is neutralized by acidosis. This blood is only toxic in the presence of a vasoconstricted, capillary dilated state and not with a normal circulation. When exposure to a large surface area,

particularly metal, glass, air or oxygen, can be avoided, as by the use of a membrane instead of disk or bubble oxygenator, it is possible to make much longer runs of extracorporeal circulation without the production of disseminated intravascular coagulation and death. It is possible to perform pump runs of 24 to 48 hr without ill effect in animals if no oxygenator is used at all.[1] This may be done by use of a special catheter which perforates the interatrial septum. Blood is then withdrawn from the heart after the animal's own lungs have oxygenated the blood and no oxygenator is necessary.

The foreign surface of an intravascular catheter incites thrombosis of the involved vessel not only because of the surface involved, but also because it serves as a site for entrance of infection through the skin. Any catheter left in place long enough will cause a thrombophlebitis, usually much sooner in the lower extremity than in the upper. It is slowest to cause thrombosis if placed in a large vessel with good flow.

CONDITION OF THE ENDOTHELIUM

Factors related to the vascular wall. The fact that injury to a vessel wall, particularly the intima, will result in an immediate accumulation of platelets with subsequent fibrin formation is well-known and well-documented.[58] With accumulation of platelets there is platelet agglutination and breakdown, with liberation of thromboplastin and fibrin accumulation. The breaks in endothelium and irregular surfaces produced by atherosclerosis are well-known in their production of thrombosis. In addition, the endothelium can be damaged by many infectious diseases such as those due to viruses and Rickettsia.[1]

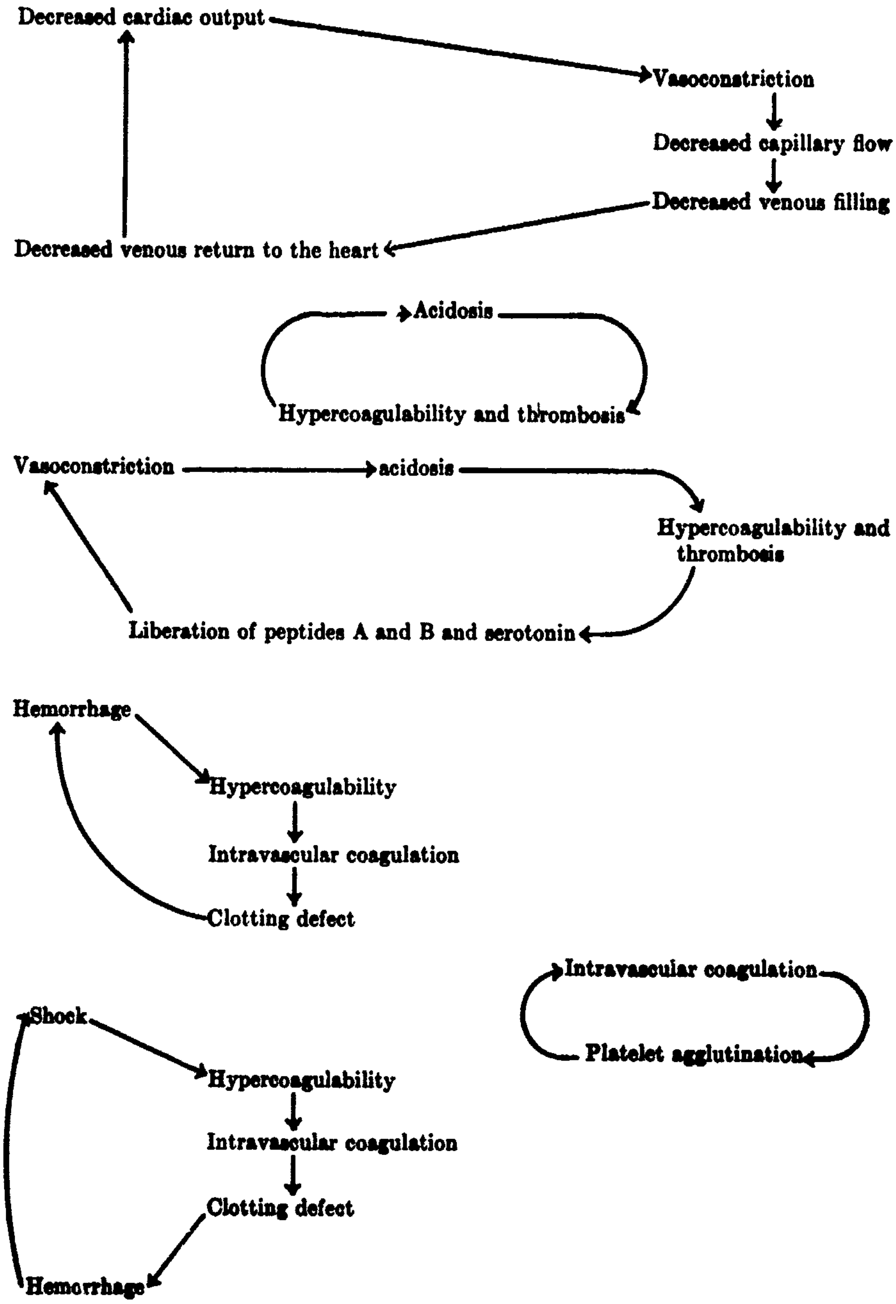
VICIOUS CIRCLES

All of the above-discussed factors which promote intravascular coagulation may have an influence on each other in a vicious circle so as to promote even more the production of intravascular coagulation. For instance, a decreased cardiac output promotes arteriolar vasoconstriction. This decreases venous return to the heart and cardiac output. This in turn promotes more vasoconstriction. Acidosis promotes hypercoagulability and thrombosis which decreases capillary flow and produces more acidosis.

Vasconstriction decreases capillary flow which promotes acidosis. Acidosis promotes coagulation which liberates vasoconstrictive substances which cause more vasoconstriction.[59] These and many others may be expressed as vicious circles (scheme 1).

PROPHYLAXIS AND THERAPY

Knowing factors which promote intravascular thrombosis, it is possible to postulate how to prevent and treat intravascular thrombosis. The most important single factor in preventing thrombosis is adequate blood flow. This can be promoted in leg and other veins by muscular motion, which, assisted by venous valves, effectively pumps the blood through the veins. Avoidance of


Decreased cardiac output
Vasoconstriction
Decreased capillary flow
Decreased venous filling
Decreased venous return to the heart
Acidosis
Hypercoagulability and thrombosis
Vasoconstriction
acidosis
Hypercoagulability and thrombosis
Liberation of peptides A and B and serotonin
Hemorrhage
Hypercoagulability
Intravascular coagulation
Clotting defect
Intravascular coagulation
Platelet agglutination
Shock
Hypercoagulability
Intravascular coagulation
Clotting defect
Hemorrhage

SCHEME 1

motionless standing, sitting or lying is important. Exercise and elevation of the legs without constriction are helpful when the patient is bedfast. Early ambulation involves exercise and promotes flow. "Dangling" of the legs over the bed should be avoided.

Blood flow can be improved by filling the vascular space, whether the vascular space is normal or increased in size. If central venous pressure is low, increased volume will enable an adequate venous return to the heart. Any physiologic fluid can be used to increase blood volume including blood, dextran or saline. In addition, low molecular weight dextran has the happy property of not only causing volume expansion and red cell dilution but of preventing red cell agglutination, an early stage in disseminated intravascular coagulation. It will inhibit thrombus formation.[60] Normal dextran also will do these things. Dextran has been successfully used to treat and prevent thrombophlebitis.[61] However, large molecular dextran has the property of causing intravascular coagulation with decrease of clotting factors and onset of coagulation defects. All dextran is a mixture of large and small molecules. Large molecules of dextran, like other particulate matter, activate factor XII, causing intravascular coagulation. Small molecules leave the blood faster than large molecules. Therefore, if repeated units of low or middle weight dextran are given over a period of several days, large molecules accumulate and may give the harmful effect of large molecular dextran.

If blood flow is deficient due to inability of a damaged heart to pump the blood, the heart may be stimulated by such drugs as digitalis, norepinephrine or Isuprel. If flow is decreased due to arteriolar constriction secondary to a high catecholamnie level, the addition of vascular volume will probably decrease it. If this is done and vasospasm persists, dibenzyline may be given to open the arterioles. Arterial blood pressure and capillary dilation can usually be corrected by means described above.

Viscosity is affected by blood flow and by hematocrit. The former may be corrected as described above, the latter by administration of adequate amounts of fluids orally and intravenously to include electrolyte solution, plasma or plasma expanders, or, in rare cases, by bleeding.[1]

The use of heparin and the cumarin compounds are classic in the treatment and prevention of thrombophlebitis and are certainly useful. However, as seen above, heparin may be completely inactivated in the presence of severe acidosis. Acidosis may be severe in the capillaries and veins when it is only nominal in the arterial blood, the usual site for pH determination.

Fibrinolysin is certainly effective in dissolving fibrin and theoretically should be useful. It is not inactivated by acidosis. However, exogenous fibrinolysin cannot get to the clot, except at its interface, with flowing blood, and so is largely ineffective. In addition, there is the danger of dislodging pieces of clot to cause pulmonary emboli.

Because of the effect of vascular spasm in encouraging thrombosis and the thrombosis-vasospasm vicious circle, a general or local blockade of the sym-

pathetic fibers may be indicated. This may be done by spinal blockade with procaine or systemically by dibenzyline (only after adequate volume addition, as determined by central venous pressure).[1]

Acidosis may be treated by administration of THAM or TRIS buffer, and bicarbonate. However, perhaps the best way to prevent and treat acidosis is by promoting an adequate capillary flow, as described above.

Bacterial infection should be treated with appropriate antibiotics and other indicated measures.

Hemolysis should be avoided if at all possible and attempts made to assist the kidneys in excreting hemolytic products as quickly as possible. Adequate urine flow will help. Trauma, extracorporeal circulation, infection and other conditions promote hemolysis.

SUMMARY AND CONCLUSIONS

1. The most important basic vascular problem is intravascular coagulation.
2. This is caused by four main groups of factors: factors causing slow blood flow; factors causing hypercoagulability; substances initiating coagulation; and damage to the vascular endothelium.
3. Knowing the ~~above~~ factors, intravascular coagulation can be minimized by various measures to prevent ~~the above~~.

REFERENCES

1. Hardaway, R. M.: *Syndromes of Disseminated Intravascular Coagulation, with Special Reference to Shock and Hemorrhage.* Charles C Thomas, Publisher, Springfield, Ill., 1966.
2. White, A. G., and Sales, J. E.: Thrombosis of the internal jugular vein in congestive heart failure. Brit. M. J., *1:* 1473, 1965.
3. Laki, K., and Gladner, J. A.: Some aspects of the fibrinogen-fibrin transition. Nature, *187:* 758, 1960.
4. Hardaway, R. M., Elovitz, M. J., Brewster, W. R., Jr., Houchin, D. N., Renzi, N. L. and Jackson, D. R.: Influence of vasoconstrictors and vasodilators on disseminated intravascular coagulation in irreversible hemorrhagic shock. Surg. Gynec. & Obst., *119:* 1053, 1964.
5. Hardaway, R. M., Brune, W. H., Geever, E. F., Burns, J. W., and Mock, H. P.: Studies on the role of intravascular coagulation in irreversible hemorrhagic shock. Ann. Surg., *155:* 241, 1962.
6. Hardaway, R. M., Elovitz, M. J., Brewster, W. R., Jr., and Houchin, D. N.: Clotting time of heparinized blood. Influence of acidosis. Arch. Surg., *89:* 701, 1965.
7. Hardaway, R. M., Brewster, W. R., Jr., and Elovitz, M. J.: The influence of vasoconstriction and acidosis on disseminated intravascular coagulation. Surgery, *59:* 804, 1966.
8. Hardaway, R. M., Neimes, R. E., Burns, J. W., Mock, H. P., and Trenchak, P. T.: Role of norepinephrine in irreversible hemorrhagic shock. Ann. Surg., *156:* 57, 1962.
9. Rutherford, R. B., West, R. L., and Hardaway, R. M.: Coagulation changes during experimental hemorrhagic shock. To be published.
10. Pechet, L., and Alexander, B.: Increased clotting factors in pregnancy. New England J. Med., *265:* 1093, 1961.
11. Penick, G. D.: Hypercoagulable state. In *Transactions of the St. Moritz Conference on Thrombosis and Hemorrhage.* International Committee on Hemostasis and Hemorrhage, 1965. To be published (1966).
12. Hardaway, R. M., Watson, H. E., and Weiss, F. H.: Alterations in blood coagulation mechanism after intra-aortic injection of thrombin. A.M.A. Arch. Surg., *81:* 983, 1960.
13. Wells, R. E., Gawronski, T. H., Cox, P. J., and Perera, R. D.: Influence of fibrinogen on flow properties of erythrocyte suspensions. Am. J. Physiol., *207:* 1035, 1964.
14. Hardaway, R. M., Johnson, D. G., Houchin, D. N., Jenkins, E. B., Burns, J. W., and Jackson, D. R.: Influence of stress on fibrinogen. J. Trauma, *4:* 673, 1964.

15. Hardaway, R. M., Johnson, D. G., Houchin, D. N., Jenkins, E. B., Burns, J. W., and Jackson, D. R.: Studies on the fibrinogen replacement rate in dogs. Ann. Surg., *160:* 835, 1964.
16. Todd, M. E., Thompson, J. H., Bowie, J. W., and Owen, C. A.: Blood coagulation during pregnancy. Proc. Staff Meet. Mayo Clin., *40:* 370, 1965.
17. McKay, D. G., De Bacalao, E. B., and Sedlis, A.: Platelet adhesiveness in toxemia of pregnancy. Am. J. Obst. & Gynec., *90:* 1315, 1964.
18. Cannon, W. B., and Mendenhall, W. L.: The hastening of coagulation by stimulating the splanchnic nerves. Am. J. Physiol., *34:* 243, 1914.
19. Cannon, W. B., and Mendenhall, W. L.: The hastening of coagulation in pain and emotional excitement. Am. J. Physiol., *34:* 251, 1914.
20. Quick, A. J., Georgatsos, J. G., and Hussey, C. V.: The clotting activity of human erythrocytes. Theoretical and clinical implications. Am. J. M. Sc., *228:* 207, 1954.
21. Hardaway, R. M., Johnson, D. G., Houchin, D. N., Jenkins, E. B., Burns, J. W., and Jackson, D. R.: Influence of trauma and hemolysis on hemorrhagic shock in dogs. J Trauma, *4(5):* 624, 1964.
22. Hellem, A. J.: Adhesiveness of human blood platelets in vitro. Scandinav. J. Clin. & Lab. Invest., *12*(Suppl. 51): 1, 1960.
23. Gaarder, A. J., Jonsen, J., Laland, S., Hellem, A., and Owren, P. A.: Adenosine diphosphate in red cells as factor of adhesiveness of human blood platelets. Nature, *192:* 531, 1961.
24. Crosby, W. H.: Studies of hemoglobinuria. In *Proceedings of the Seventh International Congress of International Society of Hematology, Rome, 1958,* Vol. II, p. 424. Grune & Stratton, Inc., New York, 1960.
25. Loeb, L.: The influence of certain bacteria on the coagulation of the blood. J. M. Res., *10:* 407, 1903.
26. Walston, H. D.: The clotting of plasma through staphylococci and their products. J. Hyg., *35:* 549, 1935.
27. Biggs, R. P., and Macfarlane, R. G.: *Human Blood Coagulation and Its Disorders,* Ed. 3, p. 334. F. A. Davis Company, Philadelphia, 1962.
28. Shwartzman, G.: *Phenomenon of Local Tissue Reactivity.* Paul B. Hoeber, Inc., New York, 1937.
29. Rodriquez-Erdmann, F.: Studies on the pathogenesis of the generalized Shwartzman Reaction. III. Trigger mechanism for the activation of the prothrombin molecule. Thrombos et diathes. haemorrhag., *XII:* 471, 1964.
30 Drye, J. C.: Personal communication, 1966.
31. Wood, S., Jr.: Experimental studies of the intravascular dissemination of ascitic V2 carcinoma cells in the rabbit with special reference to fibrinogen and fibrinolytic agents. Bull. Swiss Acad. M. Sc., *20:* 92, 1964.
32. McKay, D. G.: *Disseminated Intravascular Coagulation. An Intermediary Mechanism of Disease.* Paul B. Hoeber, Inc., New York, 1965.
33. Robbins, J., and Stetson, C. A.: Mechanisms of antigen-antibody reactions upon blood coagulation. Fed. Proc., *18:* 2333, 1959.
34. McKay, D G., Shapiro, S. S., and Shanberge, J. N.: Alterations in the blood coagulation system induced by bacterial endotoxin. II. *In vitro.* J. Exper. Med., *107:* 369, 1958.
35. Schland, H A.: Shwartzman phenomenon. II. Suppressive action of nitrogen mustard on antigen-antibody provocation. Proc. Soc. Exper. Biol. & Med., *79:* 639, 1952.
36. Stetson, C A., Jr.: Studies on the mechanism of the Shwartzman phenomenon: Similarities between reactions to endotoxins and certain reactions of bacterial allergy. J. Exper. Med., *101:* 421, 1955.
37. Shwartzman, G.: Phenomenon of local skin reactivity to serum precipitates. Proc. Soc. Exper Biol. & Med., *29:* 193, 1931.
38. Shwartzman, G.: Phenomenon of local skin reactivity to bacterial filtrates: Its relation to anaphylatoxins, Forssman antibodies, and serum toxicity. J Infect. Dis, *61:* 293, 1937.
39. McCluskey, R. T, Benacerraf, B., Potter, J L, and Miller, F.: The pathologic effects of intravenously administered soluble antigen-antibody complexes. I. Passive serum sickness in mice. J. Exper. Med., *111:* 181, 1960.
40 Nakai, H and Margaretten, W.: Effect of staphylococcal toxin on the rabbit kidney. Fed Proc., *21:* A-36, 1962.
41. Sheehan, H. L. and Davis, J. C.: Renal ischaemia with failed reflow. J. Path. & Bact., *78:* 105, 1959.
42. Amundsen, M A., Spittell, J. A., Jr., Thompson, J. H., Jr., and Owen, C. A., Jr.: Hypercoagulability and malignancy. Ann. Int. Med, *58:* 608, 1963.
43. Nilsson, I. M., Krook, H., Sternby, N. H., Söderberg, E., and Söderstrom, N.: Severe thrombotic disease in a young man with bone marrow and skeletal changes and with

a high content of an inhibitor in the fibrinolytic system. Acta med. scandinav., *169:* 323, 1961.
44. Golub, S.: Bleeding in the surgical patient. Ann. New York Acad. Sc., *115:* 299, 1964.
45. Sherry, S., Fletcher, A. P., and Alkajaersig, N.: Fibrinolytic bleeding and its management. Ann. New York Acad. Sc., *115:* 481, 1964.
46. Naeye, R. L.: Thrombotic state after a hemorrhagic diathesis, a possible complication of therapy with epsilon caproic acid. Blood, *XIX:* 694, 1962.
47. Fletcher, A. P., Alkajaersig, N., and Sherry, S.: Fibrinolytic mechanism and the development of thrombolytic therapy. Am. J. Med., *33:* 738, 1962.
48. Fisher, L. M., Kagan, E., and Kupfer, H. G.: Blood coagulation changes in rats fed high fat diets. Circulation Res., *XIII:* 529, 1963.
49. Lee, K. T., Kim, D. N., and Nam, S. C.: Thrombogenic diets and blood coagulation. Fed. Proc., *21:* 438a, 1962.
50. Mustard, J. F.: Increased activity of the coagulation during alimentary lipaemia: Its significance with regard to thrombosis and atherosclerosis. Canad. M. A. J., *77:* 308, 1957.
51. Vroman, L.: Effects of hydrophobic surfaces upon blood coagulation. Thrombos. et diathes. haemorrhag., *X:* 455, 1964.
52. Hubbard, D. and Lucas, G. C.: Ionic charges of glass surfaces and other materials and their possible role in the coagulation of blood. J. Appl. Physiol., *15:* 265, 1960.
53. Eichelberger, J. W., Jr.: *Laboratory Methods in Blood Coagulation.* Paul B. Hoeber, Inc., New York, 1965.
54. Hardaway, R. M., Johnson, D. G., Houchin, D. N., Jenkins, E. B., Burns, J. W., and Jackson, D. R.: The influence of extracorporeal handling of blood on hemorrhagic shock in dogs. Exper. Med. & Surg., *23:* 28, 1965.
55. Ratnoff, O. D., and Rosenblum, J. M.: Role of Hageman factor in the initiation of clotting by glass. Evidence that glass frees Hageman factor from inhibition. Am. J. Med., *25:* 160, 1958.
56. Ratnoff, O. D., and Davie, E. W.: The activation of Christmas factor IX by activated plasma thromboplastin antecedent (factor XI). Biochemistry, *1:* 677, 1962.
57. Davie, E. W., and Ratnoff, O. D.: Waterfall sequence for intrinsic clotting. Science, *145:* 1310, 1964.
58. Berman, H. J.: The hamster cheek pouch. Intravascular phenomena. In *Proceedings of the Seventh Conference on Microcirculatory Physiology and Pathology,* p. 68. 1959.
59. Hardaway, R. M., McKay, D. G., and Hollowell, O. W.: Vascular spasm and disseminated intravascular coagulation. Influence of the phenomena one on the other. Arch. Surg., *83:* 173, 1961.
60. Sawyer, R. B., and Moncrief, J. A.: Dextran specificity in thrombus inhibition. Arch. Surg., *90:* 562, 1965.
61. Cox, E. F., Flotte, C. T., and Buxton, R. W.: Dextran in the treatment of thrombophlebitis. Surgery, *57:* 225, 1965.
62. McKay, D. G., Hardaway, R. M., Wahle, G. H., Edelstein, R., and Tartock, D. E.: Alterations in blood coagulation mechanism after incompatible blood transfusion. Am. J. Surg., *89:* 583, 1955.
63. Shayer, R. W.: *Induced Histamine and the Mechanism of Action of the Adrenal.* National Research Council Committee on Shock. 1962.
64. Shayer, R. W.: Significance of induced synthesis of histamine in physiology and pathology. Chemotherapia, *3:* 128, 1961.